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Olson & Cepuritis, LTD.
20 NORTH WACKER DRIVE
36TH FLOOR
CHICAGO, IL 60606

EXAMINER	
STEADMAN, DAVID J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,766	BRACEY ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *3-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 May 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-39 are pending in the application.

Election/Restriction

[2] Applicant's election without traverse of Group I, claims 1-2 in the reply filed on 6/16/08 is acknowledged.

[3] Claims 3-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 6/16/08.

Claim to Priority

[4] The instant application is a national stage filing under 35 U.S.C. 371 of PCT/US03/36125, filed on 11/14/03, which claims priority under 35 U.S.C. 119(e) to provisional application 60/426,788, filed on 11/14/02.

[5] Applicant's claim to domestic priority is set forth in the application data sheet filed on 5/12/05.

[6] Claims 1-2 of the provisional application appear to provide descriptive support for claims 1-2 herein.

Information Disclosure Statement

[7] All references cited in the IDS filed on 4/16/07 have been considered by the examiner. A copy of Form PTO Form 1449 is attached to the instant Office action.

[8] If the examiner has inadvertently overlooked an IDS in the application file, applicant is kindly requested to alert the examiner to this oversight in the response to this Office action.

Specification/Informalities

[9] The listing of references in the specification at pp. 26-27 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

[10] The specification and drawings are objected to as failing to comply with the requirements for a sequence listing. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If

these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly Figure 4 and specification at pp. 21-24, disclosing a list of atomic coordinates representing an amino acid sequence. Applicant should identify the disclosed sequence(s) by proper sequence identifier(s).

Claim Objection

[11] Claim 2 is objected to as reciting the improper sequence identifier "SEQ. ID. NO.1," which should be replaced with "SEQ ID NO:1." See 37 CFR 1.821(d).

[12] Claim 2 is objected to in the recitation of "said enzyme" and in order to improve claim form and maintain consistency, it is suggested that the noted phrase be replaced with, for example, "said FAAH".

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[13] Claim(s) 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

CLAIM INTERPRETATION: According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

Claim 1 is drawn to a genus of crystallized mammalian FAAH polypeptides. The specification defines "fatty acid amide hydrolase" as including any protein from any mammalian source that displays a catalytic activity to hydrolyze the amide bond of fatty acid amides and which further contains the amidase signature (AS) sequence (specification at p. 6, paragraph 24). Although the specification, in stating "from any mammalian source" appears to suggest that the FAAH has the sequence of a naturally-occurring polypeptide, it is noted that the specification discloses a crystal of an N-terminally truncated rat FAAH (specification at p. , paragraph), and thus the genus of mammalian FAAH polypeptides would appear to encompass at least deletion variants. The specification does not appear to define what is intended as being encompassed by "amidase signature sequence". The claim has been interpreted as encompassing

crystalline polypeptides in the apo-form or complexed with ligand(s). The crystallized mammalian FAAH is unlimited with respect to space group and unit cell dimensions and according to the specification, "FAAH crystals may be expected to take a wide variety of forms, all of which are included in the present invention" (p. 7, paragraph [0028]).

Claim 2 limits the FAAH of claim 1 to having "an amino acid sequence of SEQ ID NO:1, or conservative substitutions thereof". In view of the recitation of the grammatically indefinite term "an" in the phrase "an amino acid sequence of SEQ ID NO:1", the FAAH of claim 2 has been broadly but reasonably interpreted as comprising any two contiguous amino acids of SEQ ID NO:1. According to the specification, "As used herein, the phrase 'conservative variations' refers to replacement of an amino acid residue by another, biologically similar amino acid residue" (p. 6, paragraph [0025]).

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention".

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings,

or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

According to MPEP 2163.I.A, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art". In this case, the claims are drawn to a genus of crystals of a mammalian FAAH, optionally wherein the FAAH has an amino acid sequence of SEQ ID NO:1 or conservative substitutions thereof, broadly, but reasonably interpreted as noted above. Here, the claim requires adequate description of at least two elements – the FAAH polypeptide and the crystal itself.

Regarding the genus of FAAH polypeptides, the recitation of "mammalian" FAAH in claim 1 fails to provide a sufficient description of the recited genus of proteins of the crystal as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *Regents of the University of California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its

definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the recited genus of mammalian FAAH proteins the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus. In view of the broad, but reasonable interpretation of claim 2 as set forth above, the above reasoning applies equally to claim 2. In this case, the specification discloses only a single representative species of a mammalian FAAH polypeptide in crystal form, *i.e.*, amino acids 30-579 of SEQ ID NO:1. Other than this single species, the specification fails to disclose any other species of the genus of mammalian FAAH polypeptides in crystalline form, which encompasses widely variant species including "any protein from any mammalian source that displays a catalytic activity to hydrolyze the amide bond of fatty acid amides and which further contains the amidase signature (AS) sequence" as defined by the specification.

Similarly with the genus of crystals, the claims fail to set forth any identifying characteristics of a mammalian FAAH crystal sufficient to visualize or identify the members of the genus. In this case, the genus encompasses widely variant species, encompassing crystals having any space group and unit cell dimensions and optionally encompassing any ligand complexed to the mammalian FAAH polypeptide. In this case, the specification fails to adequately disclose even a single representative species of a

crystallized mammalian FAAH polypeptide. However, the prior art reference of Hanson (Dissertation, "Fatty Acid Amide Hydrolase: Structural Determination, Molecular Adaption and Biophysical Analysis", September, 2002) discloses three representative species of mammalian FAAH crystals, *i.e.,* a crystal of SEQ ID NO:1 in complex with methoxy arachidonyl fluorophosphonate and having space group $P2_1$ and the unit cell dimensions a=147Å, b=270Å, c=147Å, α=90° β=115°, and γ=90°, or space group $C222_1$ and the unit cell dimensions a=145Å, b=250Å, c=300Å, α=90° β=90°, and γ=90°, or space group $P6_322$ and the unit cell dimensions a=157Å, b=157Å, c=193Å, α=90° β=90°, and γ=120°. Other than these prior art species, the specification and prior art fail to disclose any other species of the genus of crystallized mammalian FAAH polypeptides, which encompasses widely variant species including crystals having any space group and unit cell dimensions and optionally comprising any ligand.

The claimed genus of crystals encompass widely variant species and given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[14] Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystal of SEQ ID NO:1 in complex with methoxy arachidonyl fluorophosphonate and having space group $P2_1$ and the unit cell dimensions a=147Å, b=270Å, c=147Å, α=90° β=115°, and γ=90°, or space group $C222_1$

and the unit cell dimensions a=145Å, b=250Å, c=300Å, α=90° β=90°, and γ=90°, or space group $P6_522$ and the unit cell dimensions a=157Å, b=157Å, c=193Å, α=90° β=90°, and γ=120° does not reasonably provide enablement for all crystals of any mammalian FAAH polypeptide as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims…and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject

matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims...claims are to be given their broadest reasonable interpretation that is consistent with the specification."

Claim 1 is drawn to a genus of crystallized mammalian FAAH polypeptides. The specification defines "fatty acid amide hydrolase" as including any protein from any mammalian source that displays a catalytic activity to hydrolyze the amide bond of fatty acid amides and which further contains the amidase signature (AS) sequence (specification at p. 6, paragraph 24). Although the specification, in stating "from any mammalian source" appears to suggest that the FAAH has the sequence of a naturally-occurring polypeptide, it is noted that the specification discloses a crystal of an N-terminally truncated rat FAAH (specification at p. , paragraph), and thus the genus of mammalian FAAH polypeptides would appear to encompass at least deletion variants. The specification does not appear to define what is intended as being encompassed by "amidase signature sequence". The claim has been interpreted as encompassing crystalline polypeptides in the apo-form or complexed with ligand(s). The crystallized mammalian FAAH is unlimited with respect to space group and unit cell dimensions and according to the specification, "FAAH crystals may be expected to take a wide variety of forms, all of which are included in the present invention" (p. 7, paragraph [0028]).

Claim 2 limits the FAAH of claim 1 to having "an amino acid sequence of SEQ ID NO:1, or conservative substitutions thereof". In view of the recitation of the grammatically indefinite term "an" in the phrase "an amino acid sequence of SEQ ID

NO:1", the FAAH of claim 2 has been broadly but reasonably interpreted as comprising any two contiguous amino acids of SEQ ID NO:1. According to the specification, "As used herein, the phrase 'conservative variations' refers to replacement of an amino acid residue by another, biologically similar amino acid residue" (p. 6, paragraph [0025]).

The nature of the invention: According to the specification, "...the present invention relates to the crystalline form of fatty acid amide hydrolase (FAAH) and the use of these crystals to determine the three-dimensional structure of this protein" (p. 1, paragraph [0002]). At the time of the invention, methods of protein crystallization were well-known in the art. However, the ability to crystallize a given protein was, at the very least, challenging and unpredictable to a skilled artisan as even minor alterations in the amino acid sequence of the polypeptide, ligand, and/or conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: According to MPEP 2164.03, "what is known in the art provides evidence as to the question of predictability...in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims".

At the time of the invention, the state of the art regarding protein crystallization to achieve a diffraction-quality crystal was difficult and highly unpredictable. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite

difficult to achieve" (p. 375) and that "The first prerequisite for solving the three-dimensional structure of a protein by x-ray crystallography is a well-ordered crystal that will diffract x-rays strongly…[w]ell-ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1999) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Also, Wiencek (*Ann Rev Biomed Eng* 1:505-534, 1999) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units…some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom).

Additionally, Buts et al. (*Acta Cryst* D61:1149-1159, 2005) teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were

expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution." Specifically, the reference of Buts *et* al. teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99% identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3).

Skarzynski et al. (Acta Cryst D62:102-107, 2006) teaches "crystals of complexes obtained by compound soaking may become damaged, change their diffraction properties or even change the space group during the soaking experiment!" (p. 103, right column, middle). Skarzynski et al. further teaches that binding of potent compounds during soaking often causes complete or partial disruption of the crystal lattice, poorly soluble compounds may interfere with the diffraction pattern of the protein crystal sample, and very often no binding is observed for active compounds, despite their potency under biochemical or biological assay conditions" (p. 104, left column, middle). The teachings of Skarzynski et al. are supported by applicant's specification, which teaches "Attempts to soak the GDP-4-keto, 6-deoxy mannose substrate or GDP into the crystals failed" (p. 15, top).

Even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. *Cell. Mol. Life Sci.* 2004, 61: 525-536) and currently there are no directed methods

which makes this process any easier or more predictable. Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see also Weber, *Methods in Enzymology*, 1997, Vol. 276, pp. 13-22). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Drenth, *supra,* Cudney, *Rigaku Journal*, 1999, Vol. 16, No. 1, pp. 1-7).

McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990) teaches (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every

protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual."

Thus, in view of these teachings, a skilled artisan would recognize there is a high level of unpredictability in making a diffraction-quality protein crystal.

Even though there is a high level of predictability, the prior art at the time of the invention (Hanson, *supra*) discloses three working examples of mammalian FAAH crystals as encompassed by the claims - a crystal of SEQ ID NO:1 in complex with methoxy arachidonyl fluorophosphonate and having space group $P2_1$ and the unit cell dimensions a=147Å, b=270Å, c=147Å, $\alpha=90^o$ $\beta=115^o$, and $\gamma=90^o$, or space group $C222_1$

and the unit cell dimensions a=145Å, b=250Å, c=300Å, α=90° β=90°, and γ=90°, or space group $P6_522$ and the unit cell dimensions a=157Å, b=157Å, c=193Å, α=90° β=90°, and γ=120° (p. 6, Table 2.1).

The amount of direction provided by the inventor; The existence of working examples: According to MPEP 2164.03, "if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling".

The specification sets forth an example describing formation of apparent diffraction-quality crystals of amino acids 30-579 of SEQ ID NO:1 in complex with methoxy arachidonyl fluorophosphonate (p. 13, paragraph [0041]). However, the specification fails to disclose the method of preparing the polypeptide and/or ligand for crystallization and further fails to disclose the conditions under which crystallization was achieved.

While it is acknowledged that a working example is not required to satisfy the enablement requirement, "Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art". See MPEP 2164.02.

Here, while the specification fails to enable even a single working example of the claimed crystal, the prior art does enable such a crystal as noted above, and thus, the specification in view of the prior art enables at least three working examples of crystals as encompassed by the claims.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention, it was not routine in the art to screen all polypeptides, in apo-form or complexed with any "ligand" under any crystallization conditions for those that will yield diffraction-quality crystals.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

[15] Claim(s) 1-2 are rejected under 35 U.S.C. 102(a) as being anticipated by Hanson (Dissertation, "Fatty Acid Amide Hydrolase: Structural Determination, Molecular Adaption and Biophysical Analysis", September, 2002) as evidenced by Patricelli et al. (*Biochemistry* 37:15177-15187, 1998; reference 15 of the IDS filed on 4/16/07; "Patricelli").

CLAIM INTERPRETATION: Claims 1-2 are drawn to a crystalline mammalian FAAH, optionally wherein the mammalian FAAH has an amino acid sequence of SEQ ID NO:1. The claims have been broadly, but reasonably interpreted as noted above.

Hanson teaches a crystal of an N-terminally truncated rat FAAH complexed with methoxy arachidonyl fluorophosphonate and having space group $P2_1$ and the unit cell dimensions a=147Å, b=270Å, c=147Å, α=90° β=115°, and γ=90°, or space group $C222_1$ and the unit cell dimensions a=145Å, b=250Å, c=300Å, α=90° β=90°, and γ=90°, or space group $P6_322$ and the unit cell dimensions a=157Å, b=157Å, c=193Å, α=90° β=90°, and γ=120° (pp. 5-7, particularly p. 6, Table 2.1). According to Hanson, the FAAH polypeptide used in the crystallization was "purified essentially as previously

described", citing the reference of Patricelli, wherein the Patricelli discloses purification of a rat FAAH . This anticipates claims 1-2 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[16] Claim(s) 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santarsiero et al. ("An approach to rapid protein crystallization using Nanodroplets", *J. Appl. Crystallograph.* 35:278-281, April 2002) in view of Cravatt et al. ("Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides", *Nature* 384:83-87, 1996; reference 5 of the IDS filed on 4/16/07; "Cravatt").

The reference of Santarsiero teaches crystallization of FAAH obtained from B. Cravatt (p. 279, column 1, 2.2 and p. 280, Figure 2). The difference between Santarsiero and the claimed invention is that Santarsiero does not teach the FAAH is a *mammalian* FAAH.

The reference of Cravatt teaches rat FAAH and a method for recombinant production thereof (pp. 84-85).

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Santarsiero and Cravatt to crystallize

the rat FAAH of Cravatt using the method of Santarsiero. One would have been motivated to do this because Santarsiero expressly teaches the FAAH used in the crystallization was obtained from Cravatt. One would have had a reasonable expectation of success to crystallize the rat FAAH of Cravatt using the method of Santarsiero because of the results of Santarsiero and Cravatt. Therefore, claims 1-2, drawn to a crystallized mammalian FAAH as described above, would have been obvious to one of ordinary skill in the art at the time of the invention.

[17] Claim(s) 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli (*supra*) in view of Amersham Protein Purification Handbook, October, 2001, p. 59 ("Amersham").

CLAIM INTERPRETATION: Claim 1 is drawn to a crystallized mammalian FAAH, which is broadly, but reasonably interpreted as encompassing a crystal comprising mammalian FAAH made by freezing an aqueous solution of a FAAH protein, *i.e.,* an ice crystal comprising a FAAH protein.

The reference of Patricelli teaches production and purification of an N-terminally truncated rat FAAH polypeptide (p. 15178, columns 1-2). The difference between Patricelli and the claimed invention is that Patricelli does not teach a *crystallized* rat FAAH.

The reference of Amersham discloses recommendations for purified proteins, specifically teaching, "Store in high concentration of ammonium sulphate (e.g. 4 M). Freeze in 50% glycerol, especially suitable for enzymes. Add stabilising agents, e.g.

glycerol (5-20%), serum albumin (10 mg/ml), ligand (concentration is selected based on the concentration of the active protein). Sterile filter to avoid bacterial growth" (p. 59).

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Patricelli and Amersham to freeze the polypeptide of Patricelli in the aqueous storage buffer taught by Amersham. One would have been motivated to do this because Amersham expressly recommends this for a purified protein. One would have had a reasonable expectation of success for freezing the polypeptide of Patricelli in the storage buffer taught by Amersham because of the results of Patricelli and Amersham. Therefore, claims 1-2, drawn to a crystallized mammalian FAAH as described above, would have been obvious to one of ordinary skill in the art at the time of the invention.

Citation of Relevant Art

[18] The art made of record and not relied upon is considered pertinent to applicant's disclosure. Mileni et al. ("Structure-guided inhibitor design for human FAAH by interspecies active site conversion", *PNAS* 105:12820-12824, 2008) teaches a crystallized "humanized" rat FAAH having space group $P3_221$ and the unit cell dimensions a=103.69Å, b=103.69Å, c=253.87Å, $\alpha=90^o$ $\beta=90^o$, and $\gamma=120^o$.

Conclusion

[19] Status of the claims:

- Claims 1-39 are pending.

- Claims 3-39 are withdrawn from consideration.
- Claims 1-2 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656